

Potential drug–drug interactions in inpatients treated at the Internal Medicine ward of Tikur Anbessa Specialized Hospital

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Purpose: Although the concomitant use of multiple drugs often increases therapeutic effectiveness, certain combinations result in unwanted drug–drug interactions (DDIs). Most interactions go unnoticed by physicians due to the absence of new clinical signs and symptoms, and because they often produce a worsening of already existing symptoms. Quantification of the occurrence of the potential DDIs is essential to prevent the harmful effects associated with interactions. This study was launched to assess the prevalence of potential DDIs in the Internal Medicine ward of Tikur Anbessa Specialized Hospital, Addis Ababa, Ethiopia.

Patients and methods: Cross-sectional data were gathered from the medical charts of 252 randomly selected patients who were admitted to the Internal Medicine ward during August 23 to October 23, 2013, and exposed to at least two concomitant drugs. Potential DDIs were identified using Medscape Drug Interaction Checker. The data were analyzed using SPSS software. Logistic regression analysis was used to determine the presence of association between variables and p -value <0.05 was considered statistically significant.

Results: At least one potential DDI was found in 78.2% of the patients. The mean number of potential interactions per patient was 3.7 ± 3.4 . Out of the 719 potential interactions identified, 49.8% were pharmacokinetic type, 44.6% were pharmacodynamic and the remaining 5.6% were unknown mechanisms. Major potential DDIs accounted for 13.1% of the whole interactions; 53.5% were moderate interactions; and the remaining 33.4% were minor interactions. Ceftriaxone, cimetidine and heparin were the three most involved drugs in major potential interactions. Prescription of five or more concomitant drugs was associated with high risk of encountering potential DDIs.

Conclusion: The findings of this study showed that the prevalence of potential DDIs among inpatients was high. Pharmacists should closely review drugs prescribed for patients and avoid dispensing combinations of drugs that may have serious DDIs.

Keywords: concomitant drugs, potential drug interactions, Tikur Anbessa Specialized Hospital, Ethiopia, pharmacokinetic interactions, pharmacodynamic interactions

Introduction

A drug–drug interaction (DDI) is an event that occurs when the effects of a drug are modified by another drug that is taken concomitantly.¹ DDIs can be classified, according to the mechanisms by which drugs interact with each other, as pharmaceutical, pharmacokinetic and pharmacodynamic.² DDIs may result in either increase or decrease in efficacy, in treatment failure, or in an increased toxicity of medications.^{3,4} However, not all potential DDIs are clinically significant.⁵

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Although the concurrent use of multiple drugs often increases therapeutic effectiveness, certain combinations are harmful.⁶ Most interactions go unnoticed by physicians due to the absence of new clinical signs and symptoms and because they often produce a worsening of already existing symptoms.⁷ DDIs sometimes go undetected because of a lack of knowledge and training, low motivation and poor attitude.⁸ The incidence of potential DDIs may be affected by different factors, such as higher number of concomitant drugs, presence of comorbidities and advanced age.⁹⁻¹¹

Although the presence of multiple physicians involved in patient management increases the quality of care through teamwork, it may also result in multiple separate prescriptions if there is low communication between the prescribers, which in turn increases the risk of inappropriate drug combinations.⁷ The presence of multiple comorbidities may increase the number of medications required for treatment of the conditions and associated DDIs.¹⁰ Because Tikur Anbessa Specialized Hospital (TASH) is a teaching hospital, patients are examined by many interns and residents, and as the largest referral hospital in Ethiopia, patients with a higher degree of morbidity and associated multiple comorbidities, from all over the country, are referred to this hospital, which may increase the risk of potential DDIs for patients treated at TASH.

Studies on the subject of DDIs have never been conducted in TASH before. Considering these facts and the fact that there were no clinical pharmacists in inpatient settings of the hospital during the study period, to detect and manage potential DDIs, it is possible to predict that DDIs may be prevalent in the inpatient settings, especially in the Internal Medicine ward since the largest number of patients with a wide range of disease conditions are admitted to the ward. This study was launched to determine the prevalence of potential DDIs in the Internal Medicine ward of TASH.

Patients and methods

The study was conducted in TASH, a tertiary hospital located in Addis Ababa, the capital of Ethiopia. The study was conducted in Internal Medicine ward from August 23 to October 23, 2013.

Cross-sectional data were gathered from the medical charts of 252 randomly selected patients who were admitted to the ward during the study period and exposed to at least two concomitant drugs. If patients who were included earlier in the study came back to the ward later during the study period, they were excluded.

The data collected included age and sex of the patients, their primary diagnoses, presence or absence of comorbidities and the list of medications prescribed concurrently. Poten-

tial DDIs were identified using Medscape Drug Interaction Checker, which is an online reference database accessed from reference.medscape.com/drug-interactionchecker. The database contains drug information updated through systematic review of major medical and pharmacy journals, US Food and Drug Administration (FDA) announcements and practice guidelines. In addition to information from the database, patient factors were also considered while recording interactions. Thus, potential DDIs identified by the database would not be recorded if measures were taken by prescribers (eg, modification of dose, route of administration and so on) upon prescription to prevent those potential interactions. Identified interactions were classified by severity as major, moderate and minor, as well as based on underlying mechanisms as pharmacokinetic, pharmacodynamic and unknown mechanisms. The data were analyzed using SPSS software v16 (SPSS Inc., Chicago, IL, USA). Logistic regression analysis was used to determine the presence of association between variables and *p*-value <0.05 was considered as statistically significant.

Letter of ethical clearance was obtained from the Ethics Committee of the Department of Internal Medicine of TASH. The need for patient consent was waived by the approving committee provided privacy and confidentiality were ensured during review of patients' charts by data collectors. Thus, the name and address of patients were not recorded in the data collection forms.

Results

Sociodemographic and clinical data

Of the total 252 patients, 136 (54.0%) were males and 116 (46.0%) were females. The patients' age ranged from 13 years to 87 years, and the mean age was 39.5 ± 18.0 years. The most frequent diagnoses were infectious diseases, cardiovascular diseases and hematologic disorders (Table 1).

Prevalence of potential DDIs

A total of 1280 medications were prescribed for 252 patients. The minimum number of concomitant drugs per patient was two and the maximum was 13. The mean number of drugs prescribed per subject was 5.1 ± 2.2 . In 20.6% of patients, four concomitant drugs were prescribed. The most-prescribed drugs were ceftriaxone (123 patients), followed by furosemide (80 patients), cimetidine (59 patients) and heparin (54 patients). Figure 1 shows the 15 most-prescribed drugs for the study subjects.

Among the 252 patients, 197 had prescriptions with at least one potential DDI, producing a prevalence value of 78.2%. Of these patients with potential DDIs, 52.8% were male and the remaining were female.

Table 1 Sociodemographic and clinical data of patients

Variables	Frequency (%)
Sex, n	
Male	136 (54)
Female	116 (46)
Age, years, mean \pm SD	39.5\pm18.0
<15	10 (4.0)
15–24	47 (18.7)
25–44	98 (38.9)
45–64	66 (26.2)
>65	31 (12.3)
Disease type	
Infectious	58 (23.0)
Cardiovascular	52 (20.6)
Hematologic	43 (17.1)
Solid tumor	5 (2.0)
Renal disease	12 (4.8)
Thromboembolic disorders	9 (3.6)
Gastrointestinal disorders	6 (2.4)
Neurologic	7 (2.8)
Liver disease	9 (3.6)
Diabetes mellitus	8 (3.1)
Stroke	22 (8.7)
Airway obstruction	6 (2.4)
Other*	15 (5.9)
Comorbidities	
Present	154 (61.1)
Absent	98 (38.9)
Number of drugs per patient, mean \pm SD	5.1\pm2.2
2–3	65 (25.8)
4–5	90 (35.7)
6–7	69 (27.4)
8–9	15 (5.9)
>9	13 (5.1)

Note: *Ascites (n=3), intracranial lesion (n=3), brain abscess (n=2), lung abscess (n=2), systemic lupus erythematosus (n=2), thyrotoxicosis (n=1), cystic fibrosis (n=1) and pleural effusion (n=1).

Out of the 1280 drugs prescribed to patients, 719 pairs were identified to have potential interactions. The mean DDI in these patients was 3.7 ± 3.4 . Almost one-third of the patients with identified potential DDIs (31.0%) had only one interaction.

Types of potential DDIs

Half of all DDIs identified in patients were pharmacokinetic interactions (358/719), whereas nearly the entire other half comprised pharmacodynamic interactions (321/719). The remaining few were interactions with unknown mechanisms (40/719).

Out of 358 pharmacokinetic DDIs identified, 67.6% were associated with one drug affecting the metabolism of the other. Interactions associated with altered excretion showed the next higher prevalence among pharmacokinetic interactions (19.8%), followed by altered distribution (9.5%) and absorption (3.1%) respectively (Figure 2).

Severity of potential DDIs

Assessment of severity of the identified DDIs was thereafter performed. Out of the identified DDIs, 94 (13.1%) were major interactions (Table 2). More than half of the DDIs (53.5%) were moderate interactions, and the remaining 240 (33.4%) were minor interactions. The mean number of major DDIs per patient was found to be 1.6 ± 1.0 . Nearly two-thirds (38/58) of patients with major potential interactions had only one DDI.

A total of 123 active substances were prescribed for the 252 patients incorporated in the study, five of which were not found in the Medscape drug interaction database. Hence,

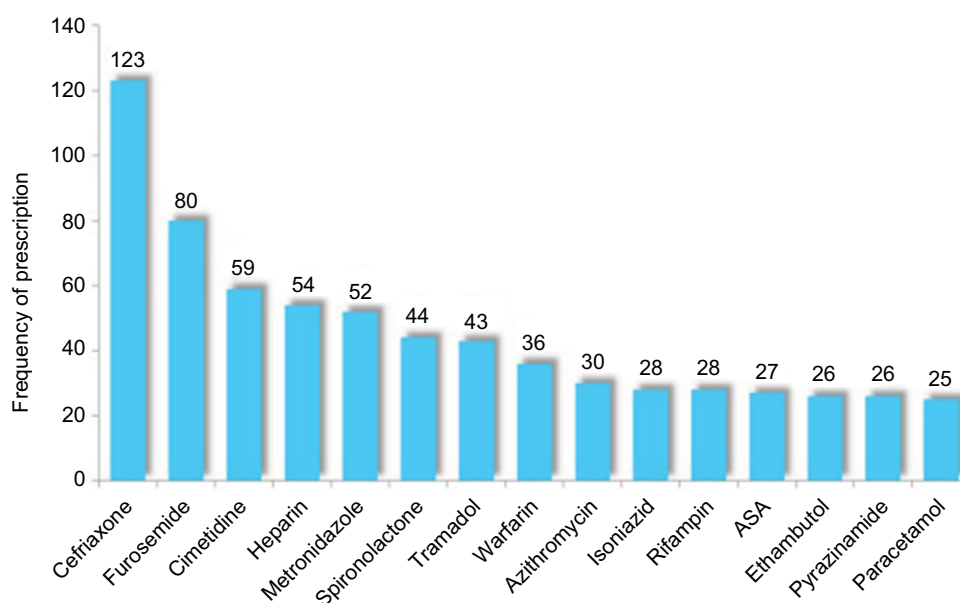


Figure 1 The most-prescribed drugs among inpatients treated at the Internal Medicine ward of Tikur Anbessa Specialized Hospital.

Abbreviation: ASA, acetylsalicylic acid

analysis was performed for ~96% of the drugs. Thus, 27 active substances accounted for 94 major DDIs. The drugs most involved in the major DDIs were ceftriaxone (30.1%), cimetidine (30.1%) and heparin (30.1%), followed by

warfarin (28.7%). When the drug classes were compared, anticoagulants were found in 54.2% of major DDIs and antibiotics were found in 52.1%.

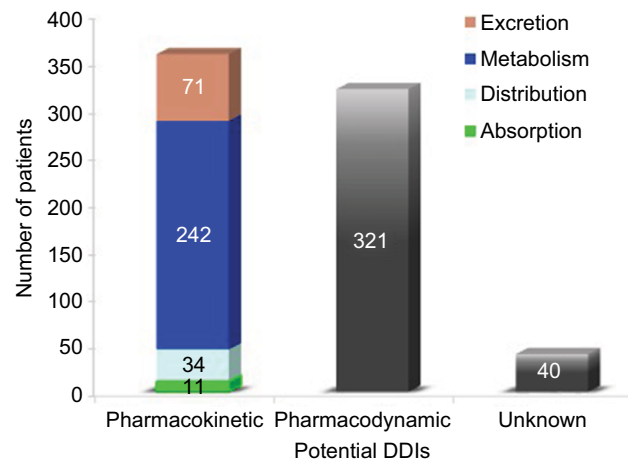


Figure 2 Types of potential drug–drug interactions (DDIs) based on the mechanism of interaction identified in patients.

Factors associated with potential DDIs

Both univariate and multivariate analyses showed that patients taking more than five concomitant drugs are at higher risk of DDIs ($p=0.000$). Both sex ($p=0.660$) and advanced age ($p=0.511$) were not significantly associated with exposure to DDIs (Table 3).

Discussion

When hospitalized patients take multiple medications, DDIs are encountered frequently. In some cases, these interactions cause adverse reactions and changes in therapeutic efficacy. This study gives important information regarding the prevalence of potential DDIs in the medical ward of TASH, their types based on the mechanism of interaction and level of severity.

Table 2 Drugs involved in major potential drug interactions

Perpetrator drug	Object drug	Frequency (%)	Mechanism of interaction	Potential outcome
Ceftriaxone	Heparin	22 (23.4)	Pharmacodynamic synergism	Increased risk of bleeding
Ceftriaxone	Warfarin	7 (7.4)	Pharmacodynamic synergism	Increased risk of bleeding
Heparin	Warfarin	7 (7.4)	Pharmacodynamic synergism	Increased risk of bleeding
Cimetidine	Dexamethasone	6 (6.4)	Inhibition of metabolism by CYP3A4	Cushing’s syndrome, adrenal insufficiency
Cimetidine	Prednisolone	5 (5.2)	Inhibition of metabolism by CYP3A4	Cushing’s syndrome, adrenal insufficiency
Cimetidine	Simvastatin	5 (5.2)	Inhibition of metabolism by CYP3A4	Liver damage, skeletal muscle injury (rare)
Cimetidine	Warfarin	5 (5.2)	Inhibition of metabolism by CYP3A4	Increased risk of bleeding
Metronidazole	Simvastatin	4 (4.2)	Inhibition of metabolism by CYP3A4	Liver damage, skeletal muscle injury (rare)
Cimetidine	Hydrocortisone	3 (3.2)	Inhibition of metabolism by CYP3A4	Cushing’s syndrome, adrenal insufficiency
Furosemide	Gentamicin	3 (3.2)	Pharmacodynamic synergism	Risk of nephrotoxicity, ototoxicity
Azithromycin	Digoxin	3 (3.2)	Increased absorption	Digoxin toxicity
Spirolactone	KCl	3 (3.2)	Pharmacokinetic synergism	Hyperkalemia
Cimetidine	Atorvastatin	3 (3.2)	Inhibition of metabolism by CYP3A4	Severe myopathy
Sulfamethoxazole	Warfarin	3 (3.2)	Competition for plasma protein binding, decreased metabolism	Increased risk of bleeding
Efavirenz	Warfarin	2 (2.1)	Inhibition of metabolism by CYP2C9/10	Increased risk of bleeding
Dexamethasone	Simvastatin	1 (1.1)	Increased metabolism by CYP3A4	Liver damage, skeletal muscle injury (rare)
Omeprazole	Digoxin	1 (1.1)	Increased absorption	Digoxin toxicity
Allopurinol	Warfarin	1 (1.1)	Decreased metabolism	Increased risk of bleeding
Cimetidine	Cyclosporine	1 (1.1)	Inhibition of metabolism by CYP3A4	Risk of nephrotoxicity and neurotoxicity
Testosterone	Cyclosporine	1 (1.1)	Decreased metabolism	Risk of nephrotoxicity and neurotoxicity
Sulfamethoxazole	Cyclosporine	1 (1.1)	Unknown mechanism	Increased nephrotoxicity
Rifampin	Warfarin	1 (1.1)	Increased metabolism by CYP3A4	Decreased effect
Amiodarone	Azithromycin	1 (1.1)	Pharmacodynamic synergism	QT interval prolongation
Amiodarone	Warfarin	1 (1.1)	Inhibition of metabolism by CYP2C9	Increased risk of bleeding
Furosemide	Paromomycin	1 (1.1)	Pharmacodynamic synergism	Increased toxicity
Nifedipine	Simvastatin	1 (1.1)	Inhibition of metabolism by CYP3A4	Liver damage
Cimetidine	Clopidogrel	1 (1.1)	Inhibition of metabolism by CYP2C19	Decreased effect
Efavirenz	Clopidogrel	1 (1.1)	Inhibition of metabolism by CYP2C19	Decreased effect
Total		94 (100)		

Abbreviation: CYP, cytochrome P450.

Table 3 Binary logistic analysis for factors associated with potential drug–drug interactions

Variables	Exposure to DDIs		OR (95% CI)	
	Exposed	Not exposed	Crude	Adjusted [#]
Sex				
Male	104	32	0.804 (0.439, 1.471)	0.864 (0.450, 1.659)
Female	93	23	1.00	1.00
Age, years				
<50	139	40	1.00	1.00
≥50	58	15	1.113 (0.571, 2.170)	1.272 (0.620, 2.611)
Number of medications				
<5	72	45	1.00	1.00
≥5	125	10	7.812 (3.712, 16.441)	7.890 (3.739, 16.651)*

Notes: [#]Adjusted for sex, age and number of medications; *significant. Bold represents significant values ($p < 0.05$).

Abbreviations: OR, odds ratio; CI, confidence interval; DDI, drug–drug interactions.

The prevalence of potential DDIs in this study was 78.2%. This figure agrees with the findings of a study in Romania, which reported a prevalence value of 78.03%.¹² Much lower prevalence values were reported by studies conducted in different settings in Thailand (27.9%) and Iran (20.3%).^{13,14} This broad difference in prevalence of potential DDIs may be explained by factors, such as difference in availability of alternative drugs and absence of clinical pharmacists and drug information software to provide drug information in the inpatient settings of TASH during the study period. Involvement of pharmacists in reviewing hospitalized patients' medication prescriptions would significantly reduce the prevalence and harmful effects of DDIs. Pharmacists contribute to better treatment outcome by early detection of medication errors, by monitoring treatment outcomes and by recommending treatment modification^{15–17}

In the present study, pharmacokinetic interactions show a little predominance over pharmacodynamic interactions, which is probably because of the high prescription frequency of drugs that affect liver enzymes, such as cimetidine and metronidazole.

In this study, the prevalence of major DDIs was 13.1%. This finding agrees with findings of studies conducted previously in other countries such as Italy and Denmark, as well as a study conducted in a different hospital in Ethiopia.^{18–20} Significantly higher incidence of major interactions was recorded in two studies conducted in other tertiary hospitals of the country^{21,22} This wide difference may be due to the difference in study population in the studies. The first study was conducted on cardiac patients, whereas the second study was on psychiatric patients, both of which involved chronic diseases treated with multiple medications.

In the present study, two-thirds of the identified DDIs come under either major or moderate category. Major DDIs are those that may be life threatening or may cause permanent

damage and hence not recommended for concomitant use, whereas moderate interactions are those that may cause deterioration of patient condition, warranting close monitoring. In contrast, minor interactions have limited clinical effect and usually require no intervention. Patients with identified major and moderate DDIs should be monitored for the potential outcomes of the interactions. These patients may need modification or alteration of therapy or dose adjustment. One-third of the potential DDIs in this study were minor interactions. These are DDIs that produce changes on effects of drugs not sufficient to precipitate clinically significant outcomes. However, minor DDIs can sometimes produce significant adverse outcomes on special populations, such as the elderly or patients with various organ failures. Close monitoring is needed for such patients even for minor DDIs. The class of drugs that were prescribed and had the largest number of major DDIs was the anticoagulants, followed by antibiotics. In this study, the frequency of involvement of drugs in major DDIs corresponds with their frequency of prescription.

No statistically significant differences were found between men and women regarding exposure to potential DDIs. Age is another important variable to consider in relation to DDIs. In this study, no statistically significant association was found between age and exposure to DDIs. The absence of association between sex and exposure to DDIs may be because the finding only indicates the potential interactions, which may be highly dependent on prescription factors than on patient factors. This explanation could also be applied for the absence of association between age and exposure to DDIs. It should be noted that although the risk of exposure to potential DDIs is similar across different age groups, the risk of actual occurrence of the interactions and the degree of morbidity due to them might not be similar.

Patients on five or more concomitant drugs were found to have higher rate of exposure to potential DDIs than those

taking less than five drugs. This is because a higher number of concomitant medications increases the probability of each drug encountering another drug with potential interaction.

The limitations of the study should not be overlooked. First, the interactions found were only potential; the presence of potential interactions does not always mean that the interactions actually occurred in the patients. The study does not attempt to determine whether the interactions actually occurred. Second, this study only covered the Internal Medicine ward, which makes the results difficult to apply for other wards such as the Pediatric ward. Despite these limitations, the findings of this study can be useful as input for understanding the extent of the problem and taking measures to improve the practice of managing drug interactions.

Conclusion

The findings of this study showed that the prevalence of potential DDIs among inpatients was high. Most of the interactions were of minor-to-moderate severity. Major DDIs are considered clinically important and should be avoided by health care professionals. Pharmacists, in particular, should closely review drugs prescribed for patients and avoid dispensing combinations of drugs that may have serious DDIs. DDI software should be introduced in the workstations of pharmacists.

Disclosure

The authors report no conflicts of interest in this work.

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